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Commonly prescribed drugs as risk factors for *Clostridioides difficile* infections: a Swedish population-based case–control study

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ABSTRACT

Background *Clostridioides difficile* infections (CDIs) are associated with antibiotic use, although the link with other drugs remains underexplored.

Objectives To investigate the association between antibiotic and non-antibiotic drugs with microbiome-modulating activity on new occurrences of CDI.

Design We conducted a Swedish population-based case–control study from 2006 to 2019 including 42 921 cases matched with 355 159 population controls on age and sex, obtained from multiple linked Swedish registries. The effect of antibiotic and non-antibiotic use within 30 days from the index date on CDI occurrence was estimated using multivariable conditional logistic regression additionally with a lasso penalty. Models were adjusted for age and sex by design and for Charlson Comorbidity Index and concomitant drug use, providing adjusted ORs (aORs) with 95% CIs.

Results Antibiotics with the greatest CDI risk were lincosamides (aOR=31.4, 95% CI 27.9 to 35.3), combinations of penicillins (aOR=19.8, 95% CI 15.9 to 24.5), sulfonamides and trimethoprim, and cephalosporins, though no association for tetracyclines. Among non-antibiotic drugs, we found decreased risks of CDI for lipid-modifiers (aOR=0.8, 95% CI 0.8 to 0.8) and aspirin (aOR=0.8, 95% CI 0.7 to 0.8) and increased risks for antidiarrhoeals (aOR=7.3, 95% CI 6.8 to 7.8), corticosteroids (aOR=2.4, 95% CI 2.3 to 2.5), proton-pump inhibitors (PPIs) (aOR=1.8, 95% CI 1.7 to 1.8), nervous system drugs, constipation drugs, histamine H2-receptor antagonists, antidepressants, and beta blockers, but no significant risk for non-steroidal anti-inflammatory drugs.

Conclusions We found varying effects of antibiotics on CDI, providing evidence for ongoing efforts in prudent prescribing decisions and antimicrobial stewardship. We confirmed PPI as a main risk factor for CDI and provided new evidence for other non-antibiotic drugs as potentially important risk factors considering their high prescription prevalence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antibiotics and gastric acid-suppressing drugs are important risk factors for *Clostridioides difficile* infection (CDI). However, the influence of other suspected microbiome-modulating drugs has not yet been investigated thoroughly.

WHAT THIS STUDY ADDS

⇒ This large, population-based cohort investigated the association of several antibiotic classes and other drugs with a suspected microbiome-modulating activity on CDI. Significantly increased odds of CDI were found for lincosamides, combinations of penicillins and sulfamethoxazole and trimethoprim, as well as several non-antibiotic drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Determining the CDI risk associated with several commonly prescribed antibiotic and non-antibiotic drugs could aid clinicians and policymakers to consider the adverse and favourable effects of these drugs.

INTRODUCTION

Clostridioides difficile infection (CDI) is the main cause of antibiotic-associated diarrhoea,[1] which develops after exposure to *Clostridioides difficile* (CD) spores and subsequent colonisation of the colon. While a healthy microbiome offers protection against CDI through colonisation resistance and bile acid regulation, changes in microbiome composition can result in uncontrolled CD growth.[2 3] This is why CDI often follows (broad spectrum) antibiotic treatment.[4] Recurrent CDI is the most common complication with increasing risk of recurrence after each infection, caused by insufficient microbiome recovery after antibiotic treatment.[5 6] Age is an important risk factor: besides a weaker immune system and frailty, this is partially attributed to a different microbiome composition comprising less protective species and an increase in opportunistic species.[6] Elderly people are also more frequently hospitalised and exposed to antibiotics and polypharmacy, and have more chronic comorbidities. Considering the central role of the microbiome in CDI, prevention and treatment strategies are focused on maintaining a healthy microbiome composition by prudent antimicrobial prescribing and microbiome restorative therapeutics.[7–10]

Evidence from large drug–microbiome interaction studies revealed that more drugs impact the gut microbiome composition than previously believed. Medication use explained most of the observed

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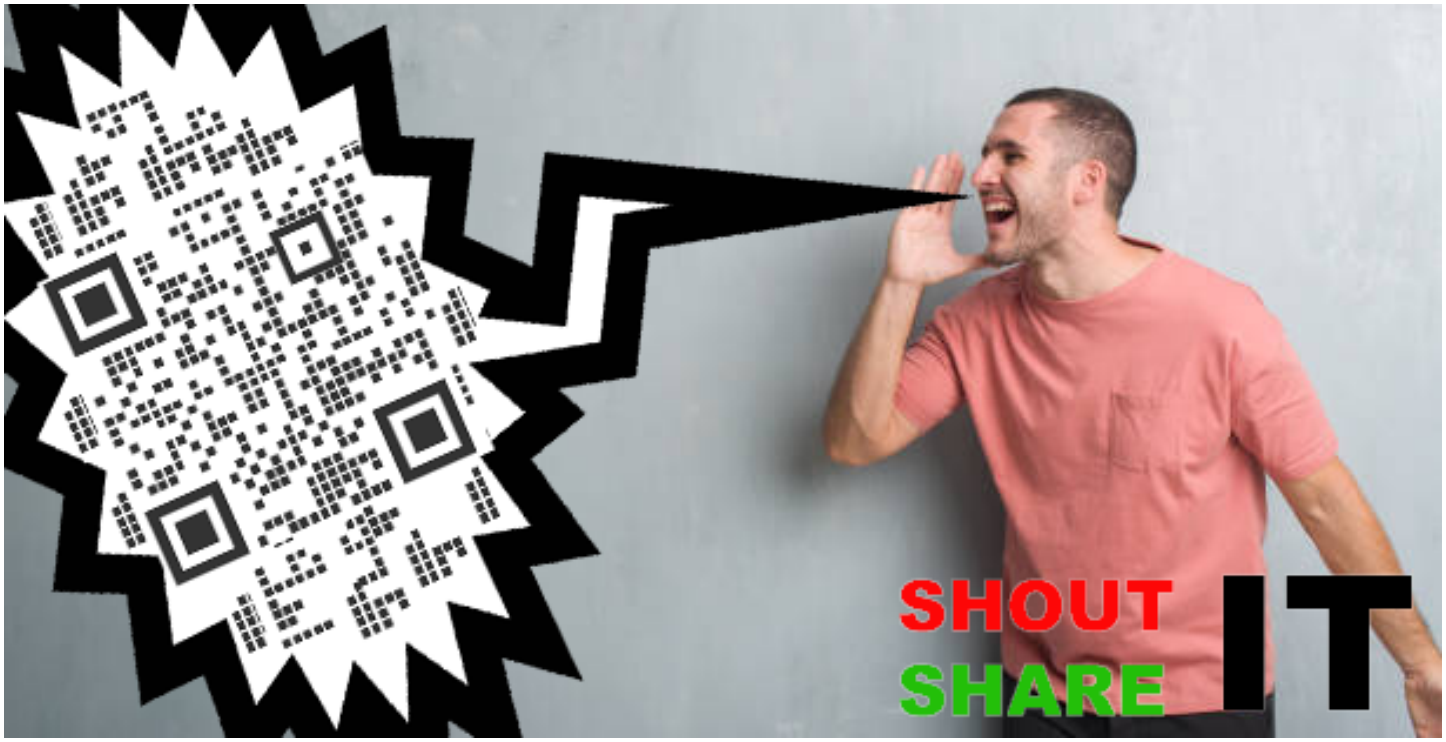
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microbiome variation in a population-level analysis.[11] Two other studies identified significant associations between the gut microbiota and almost half of the considered medication categories,[12] and common prescription drugs.[13] A recent study additionally established long-term microbiome alterations associated with prior use of 78 of the 186 tested drugs.[14] Although these studies have limitations in distinguishing drug- vs disease-driven microbiome changes, evidence from in vitro research suggests that the impact of drugs on microbial diversity cannot be discounted, as 24% of the more than 1000 tested drugs inhibited the growth of at least one strain.[15] While research has mainly focused on gastric acid suppressant drugs, proton-pump inhibitors (PPIs) and H2RAs, and somewhat on non-steroidal anti-inflammatory drugs (NSAIDs), the impact of other suspected microbiome-modulating drugs on CDI risk remains unknown.[5]

Despite novel developments and promising therapies, the burden of CDI remains high and the identification of relevant, modifiable risk factors is warranted. The shifted focus towards the microbiome and emerging evidence on the interplay with commonly prescribed drugs urges us to further investigate its role in the development of CDI. Therefore, we aim to explore the association between incidental CDI and several prescription drugs with suggested potential for microbiome modulating activity.

METHODS

Study design, setting and data sources

In this population-based case–control study, data from the Swedish National Patient registry were used to extract information from all individuals with a CDI episode between 1 January 2006 and 31 December 2019. More detailed descriptions of this cohort are available in earlier work.[16–19] We included cases with a first diagnosis of CDI defined by the 10th version of the International Classification of Diseases (ICD-10) code A04.7 and individually matched to 10 controls based on year of birth and sex. Controls were defined as not having had a CDI episode since 1997 with at least one dispensed drug prescription between 2006 and 2019 as determined by the Swedish Prescribed Drug Registry. All included cases additionally had at least one dispensed drug prescription. Demographical information was retrieved from the Swedish National Patient registry, namely age, sex and underlying morbidities that were used to calculate the Charlson Comorbidity Index (CCI) score (online supplemental table 1). We further classified CDI into likely hospital-acquired (diagnosis during or within 4 weeks after latest hospitalisation), community-acquired (diagnosis exceeding 12 weeks after latest hospitalisation) or of unknown origin (between 4 and 12 weeks after latest hospitalisation). Information on prescription drug use was retrieved from the Swedish Prescribed Drug Registry, containing information on outpatient drug use utilising Anatomical Therapeutic Classification (ATC) codes. The final cohort of 42 921 cases and 355 159 controls is smaller than described earlier,[18] because we excluded 229 unmatched cases whose 76 348 corresponding controls died before the index date, and 2 cases with 13 corresponding controls who died before their diagnosis (figure 1). We followed the Strengthening the Reporting of Observational Studies in Epidemiology and RECORD (REporting of studies Conducted using Observational Routinely-collected Data) reporting guidelines for case–control studies.[20]

Exposure: 30-day prescription drug use

Based on the ATC classification, we included all available outpatient antibiotic classes (online supplemental table 2a) and 12 non-antibiotic drug groups (online supplemental table 2b). We were limited in the selection of non-antibiotic drugs due to accessibility restrictions by the National Board of Health and Welfare and ordered information of commonly prescribed drugs with suspected microbiome-modulating activity based on available evidence at the time of study design. Exposure was defined as having at least one outpatient prescription, counting from the dispense date onwards, within 30 days preceding the first CDI episode for cases or the corresponding index date for controls.

Data analysis

Conditional logistic regression (CLR) was used to investigate the association between drug use and the first CDI episode. Univariable logistic regression was applied for each drug separately. Those with a statistically significant result at 5% significance level after Bonferroni correction were included in the multivariable analysis.

We took three different multivariable approaches to assess consistency with different assumptions: the first approach assumes each drug is associated with both the exposure and outcome, resulting in one complete multivariable model including all drugs and CCI as confounders. The second approach assumes only antibiotics and PPIs are associated with CDI, as previously described in the literature,[5] which resulted in multiple models: separate models for each non-antibiotic drug, including all antibiotics, CCI and PPIs as confounders. The third approach, which was adapted from a different study,[21] also assumes only antibiotics and PPIs are associated with CDI and combines exposure to any of these drugs into one binary exposure variable *D*. If the drug under investigation is an antibiotic or PPI, it is not included in the calculation of the exposure variable. This exposure variable and CCI were confounders in the separate models for each drug. Note that all models, including the univariable models, were controlled for age and sex by design through matching (online supplemental table 3).

Additionally, we applied a lasso penalty to the complete multivariable approach. Penalised regression can be useful in low-dimensional settings to improve the estimation of low-prevalence risk factors[22]: coefficient shrinking in the lasso model reduces overfitting and improves generalisability, at the expense of a slight increase in bias. We enforced an L1 penalty to shrink these coefficients using the clogitL1 package in R for CLR with elastic net penalties. This penalty enables the model to force coefficients to zero, which facilitates interpretation. This is particularly useful when not all predictors are expected to be associated with CDI. We performed 10-fold cross-validation with the default settings of a grid of 100 lambda values to select the best value for lambda. We selected lambda corresponding to the lowest cross-validation error ($\lambda=0.84$) and within 1 SE from the lowest cross-validation error ($\lambda=80.37$) to reduce model complexity according to the one-standard error rule. ORs were computed by exponentiating the coefficients.

Finally, we used Miettinen's formula to calculate the confounding-adjusted population attributable fraction (PAF) for ORs above one and an adjusted formula to calculate the prevented fraction for ORs below one.[23]

To assess the effect of sex, we repeated all analyses stratified by sex. All multivariable analyses were additionally restricted to cases with healthcare-associated CDIs (HA-CDIs) and their matched controls to investigate the effect of empirical treatments. This effect was additionally explored by studying the influence of several negative-control exposure windows of 5–30 days, 31–60 days and 61–180 days prior to the index date on the risk of CDI.

All analyses were stratified by calendar periods (2006–2010, 2011–2015, 2016–2019) to investigate secular trends. A

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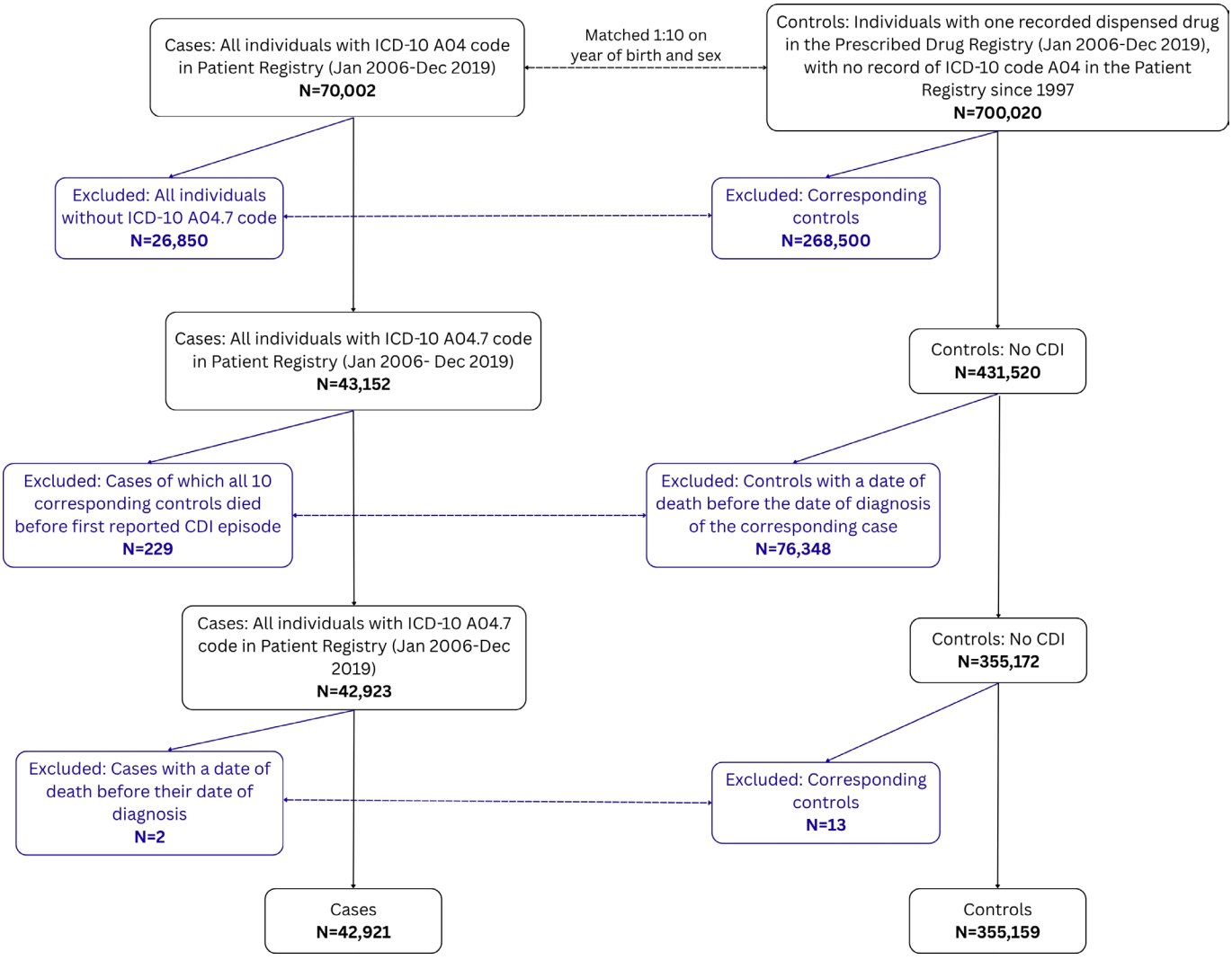
Cases: All individuals with ICD-10 A04 code in Patient Registry (Jan 2006-Dec 2019)
N=70,002
Matched 1:10 on year of birth and sex
Controls: Individuals with one recorded dispensed drug in the Prescribed Drug Registry (Jan 2006-Dec 2019), with no record of ICD-10 code A04 in the Patient Registry since 1997
N=700,020
Excluded: All individuals without ICD-10 A04.7 code
N=26,850
Excluded: Corresponding controls
N=268,500
Cases: All individuals with ICD-10 A04.7 code in Patient Registry (Jan 2006- Dec 2019)
N=43,152
Controls: No CDI
N=431,520
Excluded: Cases of which all 10 corresponding controls died before first reported CDI episode
N=229
Excluded: Controls with a date of death before the date of diagnosis of the corresponding case
N=76,348
Cases: All individuals with ICD-10 A04.7 code in Patient Registry (Jan 2006-Dec 2019)
N=42,923
Controls: No CDI
N=355,172
Excluded: Cases with a date of death before their date of diagnosis
N=2
Excluded: Corresponding controls
N=13
Cases
N=42,921
Controls
N=355,159

Figure 1 Study population flow chart. CDIs, *Clostridioides difficile* infections; ICD-10, International Classification of Diseases,10th edition.

secondary analysis including length of hospital stay, number of admissions and outpatient visits within 180 days prior to the index date was conducted to adjust for baseline healthcare utilisation. To study the effect of incidental drug exposure, we have repeated the complete multivariable models excluding those with maintenance use of the drug under investigation, which was defined as having at least 2 prescriptions between 31 and 180 days prior to the index date.

RESULTS

The study population consisted mostly of elderly people and women (table 1). Age and sex distributions slightly differed between cases and controls due to variations in the number of controls per case (1–10) (online supplemental table 4). Most infections were hospital-acquired (91.57%). The case population was less healthy than the control population, with overall higher CCI scores among cases (table 1). All drug prevalences were higher among cases than controls.

Drug prevalences

While all antibiotics were more prevalent among cases than controls, this difference was extreme in nitroimidazole derivatives and intestinal anti-infective antibiotics (table 1). Additionally, large relative differences were observed for lincosamides, combinations of penicillins and fluoroquinolones. All cephalosporins and carbapenems were grouped together (ATC J01D), and other aminoglycosides, glycopeptide antibacterials and polymyxins were removed due to very low prevalence (online supplemental table 2a).

All non-antibiotic drug groups were frequently dispensed among cases, except H2RAs. Large differences in exposure with the controls were prominent for antidiarrhoeals (table 1). Antiepileptic drugs (ATC N03) and psycholeptic drugs (ATC N05) were grouped to remove multicollinearity.

Univariable and multivariable models

All drugs had strong associations with CDI in the univariable analysis (table 2), across all sexes (online supplemental table 5), thus were included in the multivariable analyses (table 2). Among these multivariable approaches, all drugs were associated with CDI and had a consistent direction of the effect, except for tetracyclines, NSAIDs and beta-blockers, which had non-significant or opposite associations with CDI (table 2). The ORs were generally smallest and hence more conservative in the complete model compared with the separate and D variable models, especially for nitroimidazole derivatives and intestinal anti-infective antibiotics (table 2). Therefore, estimates from this

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Table 1 Study population characteristics of cases (N=42 921) and matched controls (N=355 159)

	Number of cases (%)	Number of controls (%)
Sex		
Male	19 655 (45.79)	159 894 (45.02)
Female	23 266 (54.21)	195 265 (54.98)
Age (years)		
Mean (SD)	71 (20)	68 (21)
Median (IQR)	76 (64, 84)	73 (61, 82)
Range	0, 105	0, 105
0–18	1673 (3.90)	16 723 (4.71)
19–40	2459 (5.73)	24 535 (6.91)
41–64	7403 (17.25)	72 545 (20.43)
65–80	16 328 (38.04)	145 884 (41.08)
80+	15 058 (35.08)	95 472 (26.88)
Source of infection		
HA-CDI	39 302 (91.57)	NA
CA-CDI	3089 (7.20)	NA
Unknown Source	530 (1.23)	NA
Charlson Comorbidity Index		
0	6093 (14.20)	144 246 (40.61)
1	5290 (12.32)	55 980 (15.76)
2	8045 (18.74)	62 296 (17.54)
3	6800 (15.84)	40 281 (11.34)
4	5231 (12.19)	22 694 (6.39)
≥5	11 462 (26.70)	29 662 (8.35)
Antibiotics		
Tetracyclines (ATC J01AA)	398 (0.93)	1692 (0.48)
Extended spectrum penicillins (ATC J01CA)	2120 (4.94)	2722 (0.77)
Beta-lactamase sensitive penicillins (ATC J01CE)	1275 (2.97)	2628 (0.74)
Beta-lactamase resistant penicillins (ATC J01CF)	2850 (6.64)	1680 (0.47)
Combination of penicillins (ATC J01CR)	789 (1.84)	184 (0.05)
Other beta-lactam antibacterials (ATC J01D)	1127 (2.63)	444 (0.13)
Trimethoprim and derivatives (ATC J01EA)	348 (0.81)	748 (0.21)
Combination of sulfonamides and trimethoprim (ATC J01EE)	1100 (2.56)	297 (0.08)
Macrolides (ATC J01FA)	163 (0.38)	297 (0.08)
Lincosamides (ATC J01FF)	2686 (6.26)	555 (0.16)
Fluoroquinolones (ATC J01MA)	3203 (7.46)	1495 (0.42)
Steroid antibacterials (ATC J01XC)	62 (0.14)	14 (<0.01)
Nitrofuran derivatives (ATC J01XE)	559 (1.30)	1112 (0.31)
Other antibacterials (ATC J01XX)	388 (0.90)	1154 (0.32)
Nitroimidazole derivatives (ATC P01AB, J01XD)	5083 (11.84)	316 (0.09)
Intestinal anti-infective antibiotics (ATC A07AA)	1106 (2.58)	6 (<0.01)
Non-antibiotics		
Beta blockers (ATC C07)	8546 (19.91)	37 543 (10.57)
Lipid modifiers (ATC C10)	4565 (10.64)	26 174 (7.37)
Systemic corticosteroids (ATC H02)	4763 (11.10)	6757 (1.90)
Non-steroidal anti-inflammatory drugs (ATC M01A)	1852 (4.31)	9340 (2.63)
Drugs for constipation (ATC A06)	2996 (6.98)	7708 (2.17)
Antidiarrhoeals (ATC A07)	5043 (11.75)	2398 (0.68)
Acetylsalicylic acid (aspirin) (ATC B01AC06)	5723 (13.33)	31 681 (8.92)
Antidepressants (ATC N06A)	6191 (14.42)	22 409 (6.31)
Analgesics (ATC N02)	9256 (21.57)	15 230 (4.29)
Anti-epileptics and psycholeptics (ATC N03, N05)	10 024 (23.35)	35 939 (10.12)
Proton-pump inhibitors (ATC A02BC)	8582 (19.99)	20 044 (5.64)
H2-receptor antagonists (H2RAs) (ATC A02BA)	216 (0.50)	746 (0.21)

CA-CDI, community-associated CDI; HA-CDI, healthcare-associated *Clostridioides difficile* infection; NA, not available.

complete model were used to conduct the lasso regression and calculate the PAFs.

Tetracyclines were the only antibiotics not associated with an increased CDI risk after adjustment for CCI and other drug use in the complete model (table 2, figure 2). Extreme ORs were found for nitroimidazole derivatives (adjusted OR (aOR)=103.03; 95% CI 89.74 to 118.30) and intestinal anti-infective antibiotics (aOR=307.50; 95% CI 119.67 to 790.15), and high ORs for lincosamides, combinations of penicillins, sulfonamides and trimethoprim, and other beta-lactam antibacterials, all with ORs above 10.

All non-antibiotic drugs, except NSAIDs, were associated with CDI. Most increased the odds of CDI, apart from lipid modifiers (aOR=0.79; 95% CI 0.75 to 0.83) and acetylsalicylic acid (aOR=0.76; 95% CI 0.73 to 0.79). We observed the highest OR for antidiarrhoeals (aOR=7.30; 95% CI 6.80 to 7.84), analgesics (OR=2.84, 95% CI 2.73 to 2.96) and corticosteroids (aOR=2.38; 95% CI 2.26 to 2.52). PPIs (aOR=1.75; 95% CI 1.68 to 1.82) and H2RAs (1.43; 95% CI 1.16 to 1.77) also showed increased odds of CDI.

Lasso regularisation

In comparison with the complete model, the simplest lasso model (λ=80.37) caused the largest OR shrinkage for the combination of penicillins (19.59 to 11.62), nitroimidazole derivatives (103.03 to 79.74) and intestinal anti-infective antibiotics (307.50 to 17.95), while tetracyclines, macrolides, steroid antibacterials, other antibacterials and H2RAs were removed from the lasso model (table 2, figure 2). Shrinkage was minimal in other non-antibiotic drugs. For lasso regression with λ=0.84, we observed only shrinkage for the estimates of the steroid antibacterials (5.42 to 4.70) and intestinal anti-infective antibiotics (307.50 to 267.03).

Population attributable fraction

The PAF of antibiotics varied strongly, ranging from 0.11% in the steroid antibacterials to 11.73% in the nitroimidazole

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Table 2 Effect of prescription drug use on the CDI risk, presented as ORs from regular univariable, multivariable conditional logistic regression (CLR) models following 3 modelling approaches, and ORs from CLR with a lasso penalty corresponding to lowest test error (λ=0.84) and test error within 1 SE from the lowest test error (λ=80.37)

Drug	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Separate OR (95% CI)	D variable OR (95% CI)	Lasso (λ=0.84): OR	Lasso (λ=80.37): OR	PAF or PF (%)
Antibiotics							
(J01AA) Tetracyclines	2.03 (1.82 to 2.27)***	0.93 (0.79 to 1.08)	1.23 (1.06 to 1.42)**	1.26 (1.10 to 1.44)***	0.93	1.00	NS
(J01CA) Penicillins extended spectrum	6.69 (6.31 to 7.10)***	4.24 (3.92 to 4.59)***	4.70 (4.36 to 5.07)***	4.41 (4.10 to 4.73)***	4.24	3.99	3.77
(J01CE) Beta-lactamase sensitive penicillins	4.24 (3.96 to 4.54)***	3.21 (2.92 to 3.53)***	3.36 (3.07 to 3.68)***	3.38 (3.11 to 3.67)***	3.21	2.88	2.05
(J01CF) Beta-lactamase resistant penicillins	14.45 (13.57 to 15.38)***	9.96 (9.17 to 10.81)***	11.55 (10.69 to 12.49)***	11.68 (10.85 to 12.57)***	9.95	9.03	5.97
(J01CR) Combination of penicillins	38.90 (33.00 to 45.85)***	19.76 (15.91 to 24.54)***	22.79 (18.49 to 28.10)***	22.26 (18.39 to 26.94)***	19.59	11.62	1.75
(J01D) Other beta-lactam antibacterials	22.31 (19.95 to 24.94)***	11.12 (9.58 to 12.89)***	12.60 (10.93 to 14.54)***	13.20 (11.56 to 15.06)***	11.07	8.64	2.39
(J01EA) Trimethoprim and derivatives	3.83 (3.36 to 4.36)***	1.89 (1.58 to 2.26)***	2.20 (1.86 to 2.60)***	2.08 (1.78 to 2.43)***	1.88	1.35	0.38
(J01EE) Comb. of sulfonamides and trimethoprim	32.91 (28.90 to 37.47)***	12.52 (10.59 to 14.80)***	15.72 (13.40 to 18.44)***	15.56 (13.38 to 18.09)***	12.46	9.14	2.36
(J01FA) Macrolides	4.91 (4.05 to 5.96)***	1.56 (1.17 to 2.08)**	1.71 (1.29 to 2.27)***	2.18 (1.72 to 2.76)***	1.54	1.00	0.14
(J01FF) Lincosamides	45.04 (40.97 to 49.51)***	31.39 (27.90 to 35.31)***	35.75 (31.88 to 40.09)***	35.35 (31.78 to 39.32)***	31.30	25.73	6.06
(J01MA) Fluoroquinolones	19.74 (18.51 to 21.05)***	7.51 (6.88 to 8.19)***	8.74 (8.04 to 9.50)***	10.73 (9.95 to 11.58)***	7.50	6.93	6.47
(J01XC) Steroid antibacterials	38.16 (21.29 to 68.37)***	5.42 (2.13 to 13.80)***	7.50 (3.07 to 18.30)***	13.77 (6.65 to 28.52)***	4.70	1.00	0.11
(J01XE) Nitrofuran derivatives	3.88 (3.50 to 4.31)***	2.08 (1.80 to 2.41)***	2.28 (1.98 to 2.61)***	2.11 (1.86 to 2.39)***	2.08	1.67	0.68
(J01XX) Other antibacterials	2.46 (2.19 to 2.77)***	1.17 (1.00 to 1.37)*	1.35 (1.17 to 1.57)***	1.20 (1.05 to 1.38)*	1.17	1.00	0.13
(P01AB/J01XD) Nitroimidazole derivatives	166.19 (147.06 to 188.82)***	103.03 (89.74 to 118.30)***	120.80 (105.55 to 138.31)***	121.84 (107.05 to 138.68)***	102.60	79.74	11.73
(A07AA) Intestinal anti-infective antibiotics	1637.91 (734.19 to 3654.01)***	307.50 (119.67 to 790.15)***	1914.92 (767.96 to 4774.86)***	1606.00 (714.33 to 3610.77)***	267.03	17.95	2.57
Non-antibiotics							
(C07) Beta-blockers	1.92 (1.87 to 1.97)***	1.17 (1.13 to 1.22)***	1.21 (1.17 to 1.25)***	1.01 (0.98 to 1.05)	1.17	1.15	2.96
(C10) Lipid-modifiers	1.43 (1.38 to 1.48)***	0.79 (0.75 to 0.83)***	0.82 (0.79 to 0.86)***	0.69 (0.66 to 0.72)***	0.79	0.82	2.79
(H02) Corticosteroids	6.31 (6.06 to 6.56)***	2.38 (2.26 to 2.52)***	3.05 (2.90 to 3.21)***	2.55 (2.43 to 2.68)***	2.38	2.33	6.44
(M01A) NSAIDs	1.77 (1.68 to 1.86)***	0.99 (0.92 to 1.06)	1.19 (1.11 to 1.27)***	1.10 (1.04 to 1.17)	0.99	1.00	NS
(A06) Constipation drugs	3.04 (2.91 to 3.18)***	1.35 (1.27 to 1.43)***	1.91 (1.81 to 2.03)***	1.73 (1.64 to 1.83)***	1.35	1.31	1.79
(A07) Antidiarrhoeals	20.11 (19.10 to 21.18)***	7.30 (6.80 to 7.84)***	8.64 (8.06 to 9.26)***	10.64 (10.01 to 11.32)***	7.30	7.22	10.14
(B01AC06) Acetylsalicylic acid	1.38 (1.34 to 1.43)***	0.76 (0.73 to 0.79)***	0.85 (0.82 to 0.89)***	0.71 (0.69 to 0.74)***	0.76	0.78	4.08
(N06A) Antidepressants	2.32 (2.25 to 2.40)***	1.16 (1.11 to 1.21)***	1.55 (1.49 to 1.61)***	1.20 (1.16 to 1.25)***	1.16	1.14	1.95
(N02) Analgesics	6.04 (5.87 to 6.22)***	2.84 (2.73 to 2.96)***	3.46 (3.34 to 3.60)***	3.11 (3.00 to 3.22)***	2.84	2.82	13.98
(N03/05) Anti-epileptics and psycholeptics	2.87 (2.80 to 2.94)***	1.50 (1.44 to 1.55)***	1.89 (1.83 to 1.95)***	1.57 (1.52 to 1.61)***	1.50	1.49	7.74
(A02BC) Proton-pump inhibitors	3.92 (3.80 to 4.03)***	1.75 (1.68 to 1.82)***	2.60 (2.51 to 2.69)***	2.52 (2.43 to 2.61)***	1.75	1.73	8.54

Continued

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Table 2 Continued

Drug	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Separate OR (95% CI)	D variable OR (95% CI)	Lasso (λ=0.84): OR	Lasso (λ=80.37): OR	PAF or PF (%)
(A02BA) Histamine H2-receptor antagonists	2.42 (2.08 to 2.82)***	1.43 (1.16 to 1.77)***	1.87 (1.53 to 2.28)***	1.93 (1.60 to 2.32)***	1.42	1.00	0.15

The univariable model is adjusted for age and sex by design and the multivariable models are additionally adjusted for Charlson Comorbidity Index and concomitant drug use.
The PAF or PF for drugs positively or negatively associated with CDI risk were calculated based on the ORs from the multivariable CLR model.
*p<0.05, **p<0.01, ***p<0.001.
CDI, *Clostridioides difficile* infection; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; PAF, population attributable fraction; PF, prevented fraction.

derivatives. Similarly, the PAF of non-antibiotic drugs varied from 0.15% in H2RAs to 13.98% in analgesics.

Sex

Similar drug associations with CDI were found across sexes, although other antibacterials and NSAIDs were not associated with CDI among women (online supplemental tables 5 and 6). Moreover, beta-lactamase resistant penicillins seemed associated with higher odds, and penicillins with extended spectrum with lower odds in women.

Empirical treatment

A sensitivity analysis was conducted including only HA-CDIs (N=39 302) and their corresponding controls (N=321 075). These results were very similar to those from the complete analysis, except for decreased OR for nitroimidazole derivatives (101 to 54) and intestinal anti-infective antibiotics (307 to 69) (online supplemental tables 7 and 8).

Sensitivity analyses on several negative-exposure windows (5–30, 31–60 and 61–180 prior to the index date) showed similar yet overall decreasing ORs for antibiotic use and mostly stable results for the non-antibiotic drug groups, except tetracyclines which were significantly associated with CDI in the two older exposure windows but not associated in the more recent exposure windows (online supplemental tables 9–11).

Calendar period

Similar drug associations were found across three calendar periods (2006–2010, 2011–2015, 2016–2019), apart from other antibacterial drugs and NSAIDs, which showed a significant association with CDI between 2016 and 2019 but no significant effect in the other periods (online supplemental tables 12–14). Increasingly stronger associations with CDI were additionally found for combinations of penicillins in the newer periods.

Baseline healthcare utilisation

A sensitivity analysis including length of hospital stay, number of hospital admissions and number of outpatient visits within 180 days prior to the index CDI showed similar results to the complete analysis, although a small yet significant association between CDI and NSAIDs was observed (online supplemental tables 15 and 16).

Incidental drug use

Similar results were additionally observed when all individuals with maintenance use of the drug under investigation were removed from the analysis, except other antibacterials which were not significantly associated with CDI in this analysis (online supplemental tables 17 and 18).

DISCUSSION

From this large, population-based study capturing all recorded patients with CDI between 2006 and 2019 in Sweden, we identified strong associations with several antibiotic and non-antibiotic drug groups. Most non-antibiotic drug groups were associated with an increased CDI risk, including antidiarrhoeals, corticosteroids, analgesics, PPIs, anti-epileptics and psycholeptics, H2RAs, constipation drugs, beta-blockers and antidepressants. A decreased risk was observed for lipid modifiers and acetylsalicylic acid, and NSAIDs were not significantly associated with CDI.

Antidiarrhoeals were associated with the largest increase in odds for CDI among the non-antibiotic drugs, yet this effect is likely biased away from the null due to reverse causality in patients receiving treatment for CDI prior to diagnosis. Nevertheless, our sensitivity analyses with several exposure windows further away from diagnosis revealed smaller yet still significantly increased odds for CDI, which might mitigate the effect of reverse causality and may suggest that the effect decreases with less recent exposure as is the case for antibiotics.[24] Notably, anti-constipation drugs were also associated with increased risks of CDI, which highlights the potential impact of drugs targeting the gastrointestinal tract on the development of CDI, as reverse causality is less likely in this association. Their effect has nonetheless not been thoroughly examined by previous research, which has largely focused on the appropriateness of *C. difficile* stool testing among patients with preceding laxative use to avoid excessive testing.[25]

The second-largest CDI increase among the non-antimicrobial drugs was observed for corticosteroids. These findings are supported by a meta-analysis and two large cohort studies investigating patients with inflammatory bowel disease,[26–28] even though more recent yet smaller studies reported decreased risks of CDI.[29–31] Their impact on CDI may be mediated through their potential for microbiome alteration[32] and immunosuppression,[33] although we cannot rule out confounding by indication, since corticosteroids are frequently used to treat exacerbations of severe conditions.[34] Confounding by indication may additionally influence the strong association between CDI and analgesics, despite similar effects being observed when adjusting for baseline healthcare burden and among older exposure windows. Furthermore, a previous meta-analysis also established an increased CDI risk associated with opioid use.[35]

Our estimates for PPIs are in line with previous research and confirm their position as an important risk factor for CDI, especially because of high prescription prevalence.[36–39] Prescription prevalence was much lower in H2RAs and was associated with a lower increase in risk than PPIs, with estimates comparable with previous research.[40] The moderate effect of PPIs compared with corticosteroids and analgesics is nonetheless unexpected, since the association between PPIs and CDI has received more

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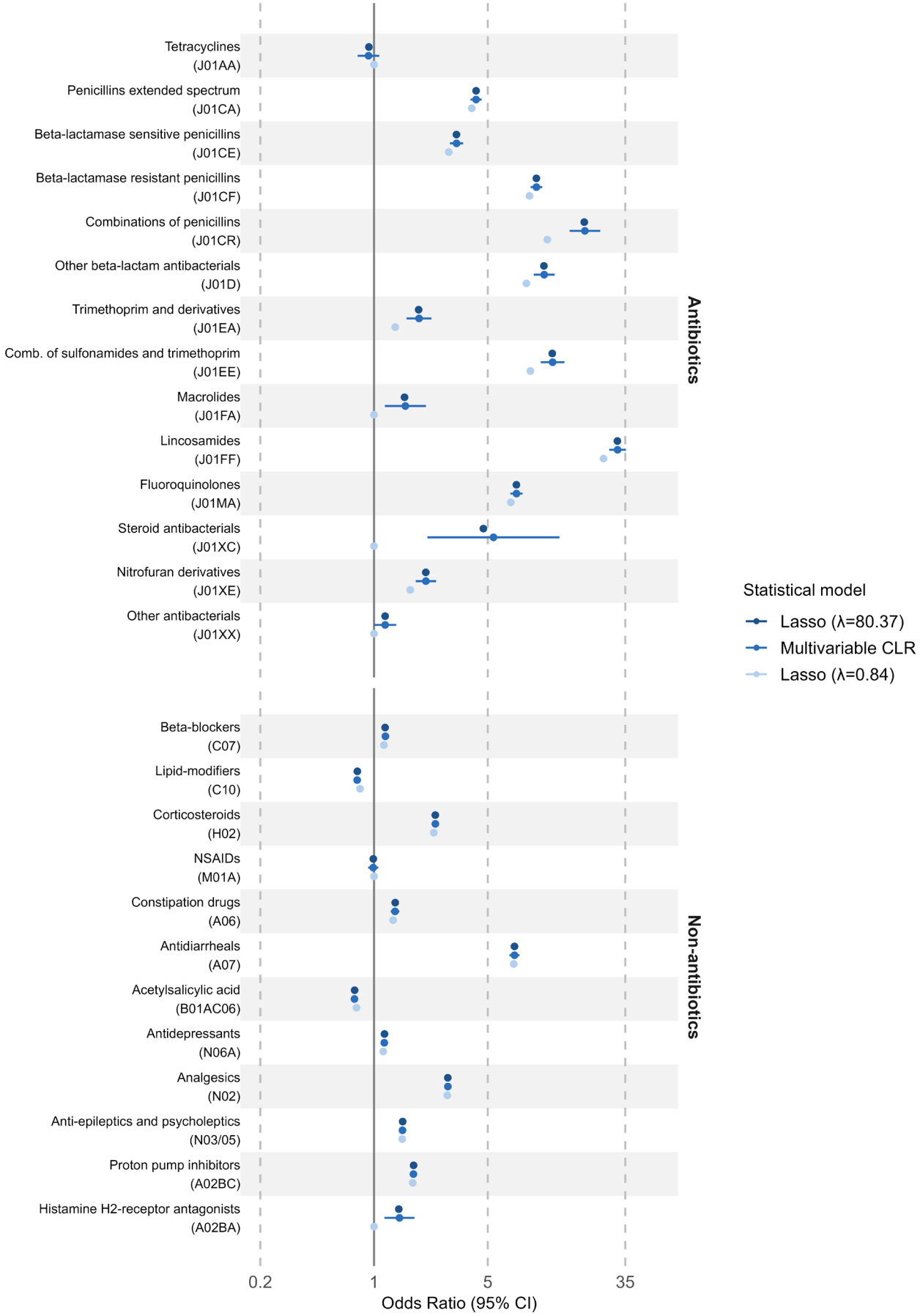

Figure 2 Forest plot. Point estimates are depicted by the circle and 95% CIs by the line segments. Exact values can be found in table 2. CLR, conditional logistic regression; NSAIDs, non-steroidal anti-inflammatory drugs.

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attention in existing literature. Though we found stable estimates across all exposure windows and even a stronger effect among incidental users, incorporating the number of prescriptions and over-the-counter prescriptions as exposures could offer further insights into the relationship between these drugs and CDI.

The effect of non-analgesic nervous system drugs on the CDI risk remains underexplored, particularly for psycholeptic and anti-epileptic drugs: we found one study describing an increased CDI risk for GABAergic drugs, a type of psycholeptic drug,[41] and one study suggesting a potential link between antiepileptic drugs and gastrointestinal adverse effects.[42] Furthermore, many studies reported mixed effects on CDI risk for different antidepressant substances,[41 43 44] even though overall no significant associations with CDI,[41] or increased risks of CDI were reported for antidepressants.[43 44] Again, these effects may reflect underlying neuropsychiatric diseases rather than the drug itself, as several studies describe associations between CDI and several neurological disorders,[45] which are potentially mediated through the gut-brain axis.

In addition, the relationship between beta-blocker use and CDI risk has received little attention in the literature, apart from some small studies describing higher prescription prevalences of beta-blockers among individuals with CDI compared with controls,[46 47] and a study finding a significant association with the gut microbiota composition.[32]

We observed a reduced CDI risk associated with lipid-modifier use, which is confirmed by previous meta-analysis reporting similar ORs for statins.[48] While we also observed a reduced CDI risk for aspirin use, a previous meta-analysis could not confirm a significant association.[26] In this study, CDI was not statistically significantly associated with NSAIDs, similar to previous research reporting no significant associations,[26 49] although others report a small increase in the risk for CDI,[50] and an association with gut microbiota.[32]

All antibiotics were associated with increased risks for CDI in this study, except for tetracyclines. Similar patterns were found in our earlier study on broader antibiotic groups,[18] apart from the significant association with tetracyclines, which may be attributed to the adjusting for the non-antibiotic drug groups.

Nitroimidazole derivatives were the predominant antibiotic class among the cases while barely prescribed in the controls, which led to an extreme OR. We made a similar observation for the intestinal anti-infective antibiotics. Both antibiotic classes are used in the treatment of CDI: metronidazole is a nitroimidazole derivative, vancomycin and fidaxomicin are intestinal anti-infective antibiotics. Consequently, reverse causality could occur when these drugs are used as empirical treatments for symptom management of CDI prior to diagnosis. We hoped to assess the effect of empirical treatments by conducting a sensitivity analysis including only HA-CDIs and their matched controls, and by investigating several negative-exposure windows. We found strong associations between both drugs and CDI across all exposure windows, and between these drugs and HA-CDI, with ORs similar to or above those of lincosamides, which are considered to be the highest-risk antibiotic class.[24 51–54]

Misclassification of HA-CDI may occur since we lacked precise timing of the CDI diagnosis during hospitalisation and applied a broader definition of HA-CDI. Confounding by indication may additionally occur when these antibiotics were prescribed for a different reason than CDI.

Lincosamides, cephalosporins, fluoroquinolones and penicillins have all been described as high-risk antibiotics.[24 51–54] Since efforts have been made in antibiotic stewardship to reduce cephalosporins and quinolones use, the prescription of combinations of penicillins has increased and consequently a growing number of studies report an association with CDI.[54 55] We additionally found a stronger association with CDI in 2016–2019 than earlier periods. Decreasing the use of combinations of penicillins should therefore be considered in antimicrobial stewardship while carefully weighing the risk of selecting other resistant organisms.

Surprisingly, the combinations of sulfonamides and trimethoprim conveyed the third-highest increase in CDI risk, whereas a large case–control study found an adjusted OR of 2.16 (95% CI 2.05 to 2.27).[24] Prior evidence described no substantial differences in the estimates for the lower-risk antibiotics trimethoprim and derivatives, macrolides and nitrofuran derivatives. Although lasso regression with $\lambda=80.37$ removed tetracyclines, macrolides, steroid antibacterials and other antibacterials from the model, this does not necessarily mean that these antibiotics are not associated with CDI considering that lasso implicitly assumes that at least some variables in the model are not associated with the outcome.[56] In fact, when the regularisation parameter is set at 0.84, none of the estimates are removed from the model. We additionally assessed the cross-deviance curve, which plots the test error for each value of lambda and showed minimal improvement in the test error with increasing regularisation, indicating that all variables contribute to the model.

Strengths of this study are the large, nationwide study design, including all reported individuals with CDI, which provided sufficient power to analyse the impact of a wide range of drug groups on the CDI risk. Furthermore, using data from high-quality registries in a matched population minimises the risk of selection and information bias. The inclusion of up to ten controls per individual with CDI further limited the impact of residual confounding. The use of the dispense date allows for a valid estimation of the exposure.

The results from this study should be applicable to populations with similar drug prescribing patterns and CDI prevalence, although differences may be observed in populations with different strains and antimicrobial resistance rates, on which this study lacks information. Furthermore, results may differ over time, although we found similar results across all investigated calendar periods.

One limitation of this study is confounding by indication or health status. Our approach to selecting controls based on at least one prescription during the study period should not have favoured more ill controls, as virtually all Swedish residents will have received at least one prescription during a 14-year period.[57] Prescription drug use was higher for cases than controls for every drug and was reflected in the CCI across both populations, which suggests poorer health among individuals with CDI compared with the controls, despite matching on age. While we controlled for CCI, this does not entirely control for confounding because the CCI is restricted to severe chronic illnesses. The observed risks of CDI could reflect general frailty or the health condition rather than the effect of the drug. This effect is likely smaller for beta-blockers where the indication (cardiovascular diseases) is included in the CCI and hence is at least partially controlled for. Furthermore, we expect a smaller influence of confounding by indication in the more distant negative-exposure windows, considering many acute conditions are typically resolved within several weeks or months. Ideally, each drug should be investigated separately with a focus on the specific exposure-outcome relationship to identify all relevant confounders and exposure-windows, which may vary between drugs with different lag periods and therapeutic windows. The duration of effect may also differ: for instance, the impact of beta-lactams may be more

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profound but shorter than the impact of macrolides and lincosamides on the microbiome.[58]

We also expect residual confounding because we did not match on hospitalisation status, drug use years before,[14] polypharmacy, smoking, genetics and diet. We tried to mitigate this by conducting a sensitivity analysis where we adjusted for length of stay, number of hospital admissions and number of outpatient visits. To limit the effect of prevalent-use bias and time-lag bias, we have performed a sensitivity analysis including only individuals with incidental drug use.

Time variation may be present for certain covariates including recent hospitalisations and disease severity. Misclassification of the outcome and selection of more severe cases may additionally occur given the limited validity of CDI diagnosis in patients, the lack of information on CDI severity from the Swedish Patient Registry, and non-mandatory reporting of CDI in Sweden. We had no information on non-antibiotic drugs beyond the restricted selection, nor on inpatient drug use, which could have impacted HA-CDIs. Finally, PAFs require careful interpretation considering their assumption of a causal relationship, which may not hold given the possibility of reverse causation and confounding by indication. Second, the PAFs cannot be summed up since they are not independent from each other and could overlap, that is, play a role in a shared causal mechanism.[59 60] Elimination of (partially) dependent risk factors will result in a lower reduction in disease than estimated by the PAF.

CONCLUSIONS

This study confirms the high impact of antibiotics on the development of CDI and presents new evidence on the elevated CDI risk shown for several non-antibiotic drugs. Given their high prevalence and strong associations with CDI, our findings underscore the importance of prudent prescribing and regular medication review of many drugs including analgesics, corticosteroids, PPIs and most antibiotic classes.

The high prescription prevalence warrants further investigation into the effect of frequently prescribed drugs on the CDI risk, including common treatments for CDI, while controlling for confounders like underlying indications, combinations of medication and over-the-counter drug use of probiotics or dietary supplements. This will support informed prescribing and optimising treatment efficacy while considering the impact on the gut microbiome.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study has been approved by the Swedish Ethical Review Authority (2020-02454), without the need for informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. The datasets generated and analysed during the current study are not publicly available due to restrictions from the National Board of Health and Welfare (Socialstyrelsen), who own the data. Data are available from the corresponding author (NB) on reasonable request after obtaining the necessary approvals from the national Ethics Committee and the National Board of Health and Welfare.

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